

University of Groningen

Scared to Death? Generalized Anxiety Disorder and Cardiovascular Events in Patients With Stable Coronary Heart Disease The Heart and Soul Study

Martens, Elisabeth J.; de Jonge, Peter; Na, Beeya; Cohen, Beth E.; Lett, Heather; Whooley, Mary A.

Published in:
Archives of General Psychiatry

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2010

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Martens, E. J., de Jonge, P., Na, B., Cohen, B. E., Lett, H., & Whooley, M. A. (2010). Scared to Death? Generalized Anxiety Disorder and Cardiovascular Events in Patients With Stable Coronary Heart Disease The Heart and Soul Study. *Archives of General Psychiatry*, 67(7), 750-758.

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Scared to Death? Generalized Anxiety Disorder and Cardiovascular Events in Patients With Stable Coronary Heart Disease

The Heart and Soul Study

Elisabeth J. Martens, PhD; Peter de Jonge, PhD; Beeya Na, MPH; Beth E. Cohen, MD, MAS; Heather Lett, PhD; Mary A. Whooley, MD

Context: Anxiety is common in patients with coronary heart disease (CHD), but studies examining the effect of anxiety on cardiovascular prognosis and the role of potential mediators have yielded inconsistent results.

Objectives: To evaluate the effect of generalized anxiety disorder (GAD) on subsequent cardiovascular events and the extent to which this association is explained by cardiac disease severity and potential behavioral or biological mediators.

Design: Prospective cohort study (Heart and Soul Study).

Setting: Participants were recruited between September 11, 2000, and December 20, 2002, from 12 outpatient clinics in the San Francisco Bay Area and were followed up until March 18, 2009.

Participants: One thousand fifteen outpatients with stable CHD followed up for a mean (SD) of 5.6 (1.8) years.

Main Outcome Measures: We determined the presence of GAD using the Diagnostic Interview Schedule. Proportional hazards models were used to evaluate the association of GAD with subsequent cardiovascular events

and the extent to which this association was explained by potential confounders and mediators.

Results: A total of 371 cardiovascular events occurred during 5711 person-years of follow-up. The age-adjusted annual rate of cardiovascular events was 9.6% in the 106 participants with GAD and 6.6% in the 909 participants without GAD ($P = .03$). After adjustment for demographic characteristics, comorbid conditions (including major depressive disorder), cardiac disease severity, and medication use, GAD remained associated with a 62% higher rate of cardiovascular events (hazard ratio, 1.62; 95% confidence interval, 1.11-2.37; $P = .01$). Additional adjustment for a variety of potential behavioral and biological mediators had little effect on this association (hazard ratio, 1.74; 95% confidence interval, 1.13-2.67; $P = .01$).

Conclusions: In outpatients with CHD, a robust association between GAD and cardiovascular events was found that could not be explained by disease severity, health behaviors, or biological mediators. How GAD leads to poor cardiovascular outcomes deserves further study.

Arch Gen Psychiatry. 2010;67(7):750-758

Author Affiliations: Department of Medical Psychology, Tilburg University, Tilburg (Drs Martens and de Jonge), Department of Psychiatry, University of Groningen, Groningen (Dr de Jonge), the Netherlands; Section of General Internal Medicine, VA Medical Center, San Francisco, California (Ms Na and Drs Cohen and Whooley); Department of Medicine, University of California, San Francisco (Drs Cohen and Whooley); and Department of Psychology, University of California, Irvine (Dr Lett).

AMPLE EVIDENCE HAS DEMONSTRATED a strong and consistent association between psychological factors, such as stress and cardiovascular health.^{1,2} These factors are important contributors to health decrements in initially healthy patients and in patients with established coronary heart disease (CHD).³ Efforts have been made to understand how these factors contribute to CHD onset, progression, and prognosis. Most of these efforts have been directed toward depression, with several meta-analyses demonstrating that depression is an independent risk factor for the development of CHD in the general population^{4,5} and a prognostic risk factor in pa-

tients with CHD.^{6,7} It is less clear whether this increased risk of cardiac events extends to patients with other symptoms of negative affect, such as anxiety.^{8,9}

Compared with the extensive literature on depression in patients with CHD, relatively few studies have examined the role of anxiety. Symptoms of anxiety are common in patients with CHD, with prevalence rates ranging from 24% to 31%.¹⁰⁻¹⁵ Several studies^{14,16,17} have found that anxiety symptoms are predictive of disability, increased physical symptoms, and worse functional status and quality of life in patients with CHD. However, studies examining anxiety as a risk factor for future CHD events have yielded conflicting results. Some studies have reported anxiety symp-

toms to be predictive of subsequent cardiac events, mortality, and in-hospital complications^{11,18-21} in patients with CHD, whereas others have found no association^{15,22-24} or even a protective effect.^{25,26} In addition, the extent to which this increased risk is independent of potential confounding factors and the role of potential mediators has not been determined. Moreover, only 1 previous study²¹ has evaluated the cardiac prognostic importance of generalized anxiety disorder (GAD); others have relied on self-report measurement of anxiety symptoms. GAD is common and treatable and could, therefore, be an important modifiable risk factor in patients with CHD.

In a prospective cohort study of 1015 participants with stable CHD, we evaluated the independent effect of GAD on subsequent cardiovascular events and the extent to which this association was explained by differences in demographic characteristics, comorbid conditions, cardiac disease severity, and potential behavioral and biological mediators.

METHODS

The Heart and Soul Study was designed to determine how psychological disorders lead to cardiovascular events in outpatients with stable CHD.²⁷ Patients in California were recruited from 2 Department of Veterans Affairs (VA) medical centers (San Francisco VA Medical Center and the VA Palo Alto Health Care System), 1 university medical center (University of California, San Francisco), and 9 public health clinics in the Community Health Network of San Francisco. Patients were eligible to participate if they had at least 1 of the following: a history of myocardial infarction, angiographic evidence of at least 50% stenosis in 1 or more coronary vessels, previous evidence of exercise-induced ischemia using treadmill or nuclear testing, a history of coronary revascularization, or a diagnosis of CHD documented by an internist or cardiologist. Between September 11, 2000, and December 20, 2002, a total of 1024 participants were enrolled: 240 from the public health clinics, 346 from the university medical center, and 438 from the VA medical centers.

All the participants completed a baseline examination that included an interview, fasting venous blood sample collection, a psychiatric interview, a questionnaire, echocardiography, exercise treadmill testing, 24-hour ambulatory electrocardiography, and 24-hour urine collection. Of the 1024 participants who completed the baseline examination, 3 did not complete the diagnostic interview for anxiety, and we could not contact 6 individuals (<1%) during follow-up, leaving 1015 for this analysis. The protocol was approved by the appropriate institutional review boards (Committee on Human Research, University of California, San Francisco; Research and Development Committee, VA Medical Center, San Francisco; Medical Human Subjects Committee, Stanford University, Stanford, California; Human Subjects Committee, Veterans Affairs Palo Alto Health Care System, Palo Alto, California; and the Data Governance Board of the Community Health Network, San Francisco). All participants provided written informed consent.

GENERALIZED ANXIETY DISORDER

We determined the presence of GAD during the past year using the computerized Diagnostic Interview Schedule for DSM-IV.²⁸ Computerized versions of the Diagnostic Interview Schedule have previously demonstrated acceptable validity and reliability.^{29,30} We also ascertained the presence of major depressive disorder (MDD) using the computerized Diagnostic Interview Schedule

for DSM-IV. Participants with a major depressive episode in the past month were informed of this diagnosis, were instructed to discuss their symptoms with their primary care physician, and were provided a list of local resources available for treatment.

BASELINE CARDIAC DISEASE SEVERITY AND RISK FACTORS

Fasting venous blood samples were collected to determine low- and high-density lipoprotein cholesterol levels. Participants completed an exercise treadmill test according to a standard Bruce protocol. Those who could not continue the standard Bruce protocol were switched to slower settings and were encouraged to exercise for as long as possible. Exercise capacity was calculated as the total number of metabolic equivalent tasks achieved. We performed resting and stress echocardiograms using an ultrasound system (Acuson Sequoia; Acuson Siemens, Mountain View, California) with a 3.5-MHz transducer. Before exercise, standard 2-dimensional parasternal long- and short-axis and apical 2- and 4-chamber views were obtained and planimetric using a computerized digitization system to determine end diastolic and end systolic left ventricular volume and to calculate left ventricular ejection fraction. At peak exercise, parasternal long- and short-axis and apical 2- and 4-chamber views were used to detect the development of left ventricular wall motion abnormalities. Inducible ischemia was defined as the presence of new wall motion abnormalities at peak exercise that were not present at rest.

POTENTIAL BEHAVIORAL MEDIATORS

Smoking and alcohol use were determined by self-report questionnaire.³¹ To assess medication adherence, we asked, "In the past month, how often did you take your medications as the doctor prescribed?" Possible responses were "all of the time (100%)," "nearly all of the time (90%)," "most of the time (75%)," "about half the time (50%)," or "less than half the time (<50%)." We defined medication nonadherence as taking prescribed medications 75% of the time or less.³² To assess physical activity, we asked, "Which of the following statements best describes how physically active you have been during the past month, that is, done activities such as 15 to 20 minutes of brisk walking, swimming, general conditioning, or recreational sports?" Participants chose 1 of the following 6 categories: not at all active, a little active (1-2 times per month), fairly active (3-4 times per month), quite active (1-2 times per week), very active (3-4 times per week), or extremely active (≥ 5 times per week). Participants who reported that they were not at all or a little active were considered physically inactive. Self-report has been shown to be a reliable, valid, and accurate method of assessing physical activity.³³⁻³⁶ In particular, single-response items have demonstrated excellent construct validity.^{35,37}

POTENTIAL BIOLOGICAL MEDIATORS

Three-channel 24-hour ambulatory Holter electrocardiography was used to assess heart rate variability,³⁸ including the standard deviation of 5-minute mean NN intervals (SDANN) and the natural log of very low frequency power. We collected 24-hour urine samples to measure norepinephrine and cortisol excretion. Norepinephrine was assessed by means of gas chromatography-mass spectrometry at Associated Regional and University Pathologists Inc (Salt Lake City, Utah). Cortisol was analyzed using radioimmunoassay or (owing to a change at the Associated Regional and University Pathologists Inc laboratory) high-performance liquid chromatography-tandem mass spectrometry.^{39,40}

Table 1. Baseline Characteristics of 1015 Participants With Stable Coronary Heart Disease by Generalized Anxiety Disorder Status^a

Variable	Anxiety (n=106)	No Anxiety (n=909)	P Value
Demographic characteristics			
Age, mean (SD), y	60 (11)	68 (11)	<.001
Male sex, No. (%)	71 (67)	761 (84)	<.001
White race, No. (%)	60 (57)	551 (61)	.42
High school graduate, No. (%)	94 (89)	789 (87)	.62
BMI, mean (SD)	29.3 (6.0)	28.3 (5.2)	.07
Comorbid conditions, No. (%)			
Major depressive disorder	85 (80)	137 (15)	<.001
Hypertension	81 (76)	637 (70)	.18
Myocardial infarction	50 (47)	495 (55)	.16
Diabetes mellitus	34 (32)	231 (25)	.14
Congestive heart failure	16 (15)	162 (18)	.50
Stroke	13 (12)	134 (15)	.51
Cardiac disease severity and risk factors			
Resting left ventricular ejection fraction, mean (SD)	0.64 (0.07)	0.61 (0.10)	.01
Exercise capacity, mean (SD), MET	7.9 (3.6)	7.2 (3.3)	.06
LDL-C, mean (SD), mg/dL	108.8 (37.8)	103.7 (33.2)	.16
HDL-C, mean (SD), mg/dL	44.2 (15.0)	46.1 (14.0)	.19
Inducible ischemia, No. (%)	18 (17)	210 (23)	.18
Medication use, No. (%)			
Aspirin	83 (78)	705 (78)	.86
β-Blocker	68 (64)	521 (57)	.18
Renin-angiotensin system inhibitor	45 (42)	477 (52)	.05
Selective serotonin reuptake inhibitor	27 (25)	70 (8)	<.001
Other antidepressant	26 (25)	52 (6)	<.001
Anxiolytic, benzodiazepine	19 (18)	64 (7)	<.001
Tricyclic antidepressant	12 (11)	32 (4)	<.001
Anxiolytic, nonbenzodiazepine	8 (8)	29 (3)	.02
Potential biological mediators, mean (SD)			
Heart rate variability, SDANN, ms	112.1 (36.7)	108.6 (36.0)	.37
Heart rate variability, lnVLF, ms ²	6.3 (0.8)	6.3 (0.9)	.93
Serotonin in non-SSRI users, ng/mL	122.8 (72.8)	119.5 (67.7)	.69
Cortisol, µg/d	34.5 (21.9)	39.0 (30.1)	.17
Norepinephrine, µg/d	51.2 (25.3)	51.8 (26.7)	.82
Log C-reactive protein, mg/L	0.65 (1.21)	0.72 (1.31)	.64
Log ω-3 fatty acid, % DHA+EPA	1.25 (0.49)	1.34 (0.43)	.05
Potential behavioral mediators, No. (%)			
Regular alcohol use	32 (30)	259 (28)	.70
Current smoking	29 (27)	170 (19)	.05
Medication nonadherence	19 (18)	64 (7)	<.001
Self-reported physical activity, No. (%)			
Not at all active	19 (18)	169 (19)	.03
A little active, 1-2 times/mo	31 (29)	151 (17)	
Fairly active, 3-4 times/mo	15 (14)	140 (15)	
Quite active, 1-2 times/wk	15 (14)	139 (15)	
Very active, 3-4 times/wk	14 (13)	202 (22)	
Extremely active, ≥5 times/wk	12 (11)	105 (12)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; lnVLF, natural log of very low frequency power; MET, metabolic equivalent task; SDANN, standard deviation of 5-minute mean NN intervals; SSRI, selective serotonin reuptake inhibitor.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; cortisol to nanomoles per liter, multiply by 27.588; C-reactive protein to nanomoles per liter, multiply by 9.524; and norepinephrine to picomoles per liter, multiply by 5.911.

^aNumbers may not sum to their respective subtotals due to missing data, and percentages may not sum to 100% due to rounding.

We used high-pressure liquid chromatography with electrochemical detection to assay whole-blood serotonin levels.⁴¹ High-sensitivity C-reactive protein (CRP) levels were measured using the Integra assay (Roche, Indianapolis, Indiana) in the first 229 participants and (owing to a change at the laboratory) the Extended Range assay (Beckman Coulter Ireland Inc, Galway, Ireland) in the remaining samples.⁴² Blood levels of 2 ω-3 fatty acids, docosahexaenoic acid and eicosapentaenoic acid, were measured using capillary gas chromatography as the percentage composition of total fatty acid methyl esters in the red blood cell membranes.⁴³

OTHER PATIENT CHARACTERISTICS

Age, sex, race, educational achievement, and medical history were determined by means of self-report questionnaire. We measured height and weight and calculated body mass index (calculated as weight in kilograms divided by height in meters squared). Participants were instructed to bring their medication bottles to their appointment, and study personnel recorded all current medications. Medications were categorized using Epocrates Rx (Epocrates Inc, San Mateo, California).

Table 2. Cardiovascular Events During Follow-up by Generalized Anxiety Disorder Status

Event	Events, Age-Adjusted Annual Rate, No. (%) ^a		Age-Adjusted Hazard Ratio (95% CI)	P Value
	Anxiety (n=106)	No Anxiety (n=909)		
Myocardial infarction	15 (3.4)	97 (1.9)	1.71 (0.98-2.99)	.06
Stroke or transient ischemic attack	7 (1.5)	42 (0.8)	1.83 (0.81-4.15)	.15
Heart failure	9 (2.0)	137 (2.5)	0.75 (0.38-1.48)	.40
All-cause mortality	24 (5.0)	242 (4.1)	1.29 (0.85-1.98)	.24
Any of these outcomes	39 (9.6)	332 (6.6)	1.43 (1.03-2.00)	.03

Abbreviation: CI, confidence interval.

^aValues represent the number of persons with anxiety and any of these specific events.

CARDIOVASCULAR EVENTS

Between the baseline examination and the last day of follow-up on March 18, 2009, we conducted annual follow-up interviews with participants (or their proxies) by telephone asking specifically about hospitalization for "heart trouble." For any reported event, medical records, electrocardiograms, death certificates, and coroner's reports were retrieved and reviewed by 2 independent blinded adjudicators. In the event of disagreement, the adjudicators conferred, reconsidered their classification, and requested consultation from a third blinded adjudicator as necessary.

The outcome events were stroke, heart failure, myocardial infarction, transient ischemic attack, and death. Heart failure was defined as hospitalization for a clinical syndrome involving at least 2 of the following: orthopnea, third heart sound, pulmonary rales, paroxysmal nocturnal dyspnea, elevated jugular venous pressure, and cardiomegaly or pulmonary edema on chest radiography. These signs and symptoms must have represented a clear change from the usual clinical status.⁴⁴ Stroke was defined as a new neurologic deficit not known to be secondary to brain trauma, tumor, infection, or another cause.^{45,46} Nonfatal myocardial infarction was defined based on the presence of symptoms, electrocardiographic changes, and cardiac enzymes using standard criteria.^{47,48} Transient ischemic attack was defined as a focal neurologic deficit (in the absence of head trauma) lasting more than 30 seconds and no longer than 24 hours, with rapid evolution of the symptoms to the maximal level of deficit in less than 5 minutes and with subsequent complete resolution.^{45,46} Deaths were confirmed by review of death certificates and coroner's reports.

STATISTICAL ANALYSIS

Baseline differences in characteristics between participants with and without GAD were compared using *t* tests and χ^2 tests. Levels of CRP and ω -3 fatty acid were log transformed because they were not normally distributed. We estimated the risk of cardiovascular events associated with anxiety disorder using Cox proportional hazards models.

To evaluate whether a covariate changed the strength of association between anxiety disorder and cardiovascular events, we calculated the percentage change in the effect size (log hazard ratio [HR]) for anxiety disorder before and after adjustment for the potential confounder or mediator. To avoid any artifact due to different sample sizes between the 2 nested models, participants missing the covariate of interest were excluded from each comparison. We sequentially considered demographic variables, including depression, comorbid conditions, cardiac disease severity, use of medications, and potential behavioral and biological mediators.⁴⁹ Variables that re-

sulted in a more than 5% change in the effect size (log HR) for GAD were considered confounders or potential mediators and were included in the final multivariable models.⁵⁰

We verified the proportional hazards assumption of these models using log-minus-log survival plots and by checking for secular patterns in scaled Schoenfeld residuals. We used Wald tests to check for interactions of anxiety disorder with age, sex, and MDD in age- and multivariable-adjusted models. Analyses were performed using a statistical software program (SAS version 9.2; SAS Institute Inc, Cary, North Carolina).

RESULTS

Of the 1015 participants, 106 (10.4%) met the criteria for GAD in the past year. Compared with participants who did not have GAD in the past year, those with GAD were younger, more likely to be female, and more likely to have MDD (**Table 1**). GAD was associated with a better left ventricular ejection fraction and greater renin-angiotensin system inhibitor, anxiolytic, and antidepressant drug use. Participants with GAD had lower ω -3 fatty acid levels and were more likely to smoke, were less physically active, and were less adherent to medications.

A total of 371 cardiovascular events occurred during 5711 person-years (mean [SD] of 5.6 [1.8] person-years) of follow-up. The age-adjusted annual rate of cardiovascular events was 9.6% in the 106 participants with GAD and 6.6% in the 909 participants without GAD (HR, 1.43; 95% confidence interval [CI], 1.03-2.00; *P* = .03) (**Table 2**). After excluding the 222 patients with MDD, the age-adjusted annual rate of cardiovascular events was 9.2% in 21 participants with GAD and 6.9% in 772 participants without GAD (HR, 1.33; 95% CI, 0.69-2.59; *P* = .39).

POTENTIAL MEDIATORS

Several variables, including male sex, comorbid conditions, left ventricular function, exercise capacity, renin-angiotensin system inhibitor and antidepressant drug use, medication nonadherence, physical activity level, heart rate variability, and CRP level, met the criteria for potential confounding or mediation (**Table 3**). Variables that did not change the effect size for GAD by 5% or more included MDD, use of selective serotonin reuptake inhibitors or anxiolytics, body mass index, smoking, and levels of serotonin, ω -3 fatty acids, and 24-hour excretion of norepinephrine and cortisol (Table 3).

Table 3. Change in the Strength of Association Between Generalized Anxiety Disorder and Cardiovascular Events^a After Adjustment for Potential Confounders and Mediators

Covariate	Change in Effect Size After Adjustment, % ^b
Demographic characteristics	
Male sex	19.7
White race	-0.2
High school graduate	0.8
Body mass index	0
Comorbid conditions	
Hypertension	-1.4
Myocardial infarction	6.4
Stroke	-2.1
Congestive heart failure	4.5
Diabetes mellitus	-9.3
Major depressive disorder	0.4
Cardiac disease severity and risk factors	
Resting left ventricular ejection fraction	31.4
Exercise capacity, MET	-13.5
LDL-C level	-0.2
HDL-C level	-2.8
Inducible ischemia	3.2
Medication use	
Aspirin	-1.2
β-Blocker	0
Renin-angiotensin system inhibitor	12.0
Tricyclic antidepressant	-10.9
Selective serotonin reuptake inhibitor	-2.5
Other antidepressant	-10.5
Anxiolytic, benzodiazepine	3.7
Anxiolytic, nonbenzodiazepine	-1.0
Potential behavioral mediators	
Regular alcohol use	-0.2
Smoking, current	-1.2
Medication nonadherence	-13.0
Physical inactivity	-17.5
Potential biological mediators	
Heart rate variability, SDANN	14.8
Heart rate variability, lnVLF	-1.4
Serotonin level, among nonusers of SSRIs	1.6
Cortisol excretion	1.9
Norepinephrine excretion	0.4
Log C-reactive protein level	10.1
Log ω-3 fatty acid level	-0.4

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; lnVLF, natural log of very low frequency power; MET, metabolic equivalent task; SDANN, standard deviation of 5-minute mean NN intervals; SSRI, selective serotonin reuptake inhibitor.

^aExpressed as the percentage change in the age-adjusted log hazard ratio.

^bChanges greater than 5% were considered clinically important and were included in subsequent multivariate regression models.

When adjusted for male sex, comorbid conditions, cardiac disease severity, and medication use, GAD remained associated with a 62% greater rate of cardiovascular events (HR, 1.62; 95% CI, 1.11-2.37; $P=.01$). Additional adjustment for potential behavioral and biological mediators, including medication nonadherence, physical inactivity, heart rate variability (SDANN), and log CRP level, did not substantially change this association (**Table 4**). In the final model, GAD was associated with a 74% greater rate of cardiovascular events (HR, 1.74; 95% CI, 1.13-2.67; $P=.01$) (**Table 5** and **Figure**). We found no evidence that the association between GAD and cardiovascular events varied by age, sex, or MDD (P for interaction $\geq .1$ for all).

Table 4. Association Between Generalized Anxiety Disorder and Subsequent Cardiovascular Events^a With Sequential Adjustment for Potential Confounders and Mediators

Adjusted Variable ^b	Hazard Ratio (95% CI)
Age, per 10-y increase	1.43 (1.03-2.00)
Plus male sex	1.54 (1.10-2.15)
Plus history of myocardial infarction and diabetes mellitus	1.56 (1.11-2.19)
Plus left ventricular ejection fraction (per 10% decrease) and exercise capacity, MET (per SD decrease)	1.72 (1.19-2.48)
Plus use of renin-angiotensin system inhibitor, tricyclic antidepressant, and other antidepressant	1.62 (1.11-2.37)
Plus potential behavioral mediators: medication nonadherence and physical inactivity	1.52 (1.04-2.24)
Plus potential biological mediators: heart rate variability (SDANN, per SD decrease) and log C-reactive protein (per SD increase)	1.74 (1.13-2.67)

Abbreviations: CI, confidence interval; MET, metabolic equivalent task; SDANN, standard deviation of 5-minute mean NN intervals.

^aCardiovascular events were heart failure, myocardial infarction, stroke, transient ischemic attack, or death.

^bEach model includes the variables from the preceding row so that the final model includes all the variables listed in this table.

Table 5. Fully Adjusted Model of the Association Between Generalized Anxiety Disorder and Subsequent Cardiovascular Events^a in 767 Participants With Complete Data on All Covariates

Variable	Hazard Ratio (95% CI)	P Value
Anxiety disorder	1.74 (1.13-2.67)	.01
Age, per 10-y increase	1.57 (1.36-1.83)	<.001
Male sex	2.47 (1.57-3.90)	<.001
History of myocardial infarction	1.50 (1.15-1.97)	.003
History of diabetes mellitus	1.38 (1.03-1.84)	.03
Left ventricular ejection fraction, per 10% decrease	1.32 (1.17-1.49)	<.001
Exercise capacity, MET, per SD decrease	1.46 (1.23-1.73)	<.001
Renin-angiotensin system inhibitor	1.13 (0.87-1.48)	.35
Tricyclic antidepressant	1.44 (0.85-2.42)	.17
Other antidepressant	1.40 (0.88-2.22)	.16
Medication nonadherence	2.83 (1.87-4.30)	<.001
Physical inactivity	1.24 (0.95-1.62)	.12
Heart rate variability, SDANN, per SD decrease	1.15 (1.00-1.33)	.05
Log C-reactive protein level, per SD increase	1.19 (1.04-1.37)	.01

Abbreviations: CI, confidence interval; MET, metabolic equivalent task; SDANN, standard deviation of 5-minute mean NN intervals.

^aCardiovascular events were heart failure, myocardial infarction, stroke, transient ischemic attack, or death.

Given that smoking is a known major cardiovascular risk factor, we conducted a sensitivity analysis by including current smoking in the final model. This did not result in a change in the effect size of GAD. In addition, adjustment for previous smoking did not change the effect of GAD. We conducted a second sensitivity analysis by including left ventricular ejection fraction as a dichotomous variable (as <45% and as ≥45%) in the final model.

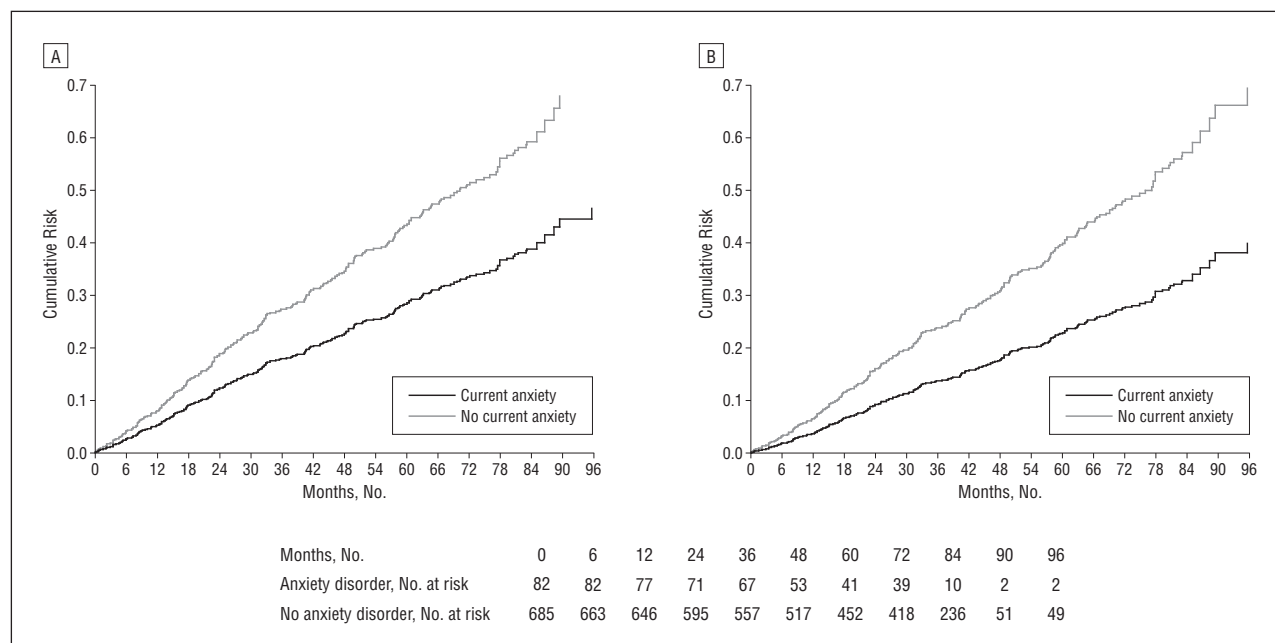


Figure. Cumulative risk of cardiovascular events stratified by the presence or absence of generalized anxiety disorder in an age-adjusted model (A) and in a model fully adjusted for potential confounders and mediators (B) in 767 participants with complete data on all covariates.

This did not result in a significant change in the effect size of GAD.

COMMENT

In this prospective cohort study of more than 1000 outpatients with stable CHD, participants with baseline GAD had a greater rate of subsequent cardiovascular events (stroke, heart failure, myocardial infarction, transient ischemic attack, or death) than did participants without GAD. Despite evaluating a variety of potential mediators, including cortisol, norepinephrine, and CRP levels; heart rate variability; smoking; medication nonadherence; and physical inactivity, the association between GAD and cardiovascular events could not be explained. Even after adjustment for these and other variables, GAD remained associated with a 74% greater rate of cardiovascular events.

This study is unique in its focus on the relationship of GAD to cardiovascular events in outpatients with stable CHD. We are aware of only 1 previous study that has evaluated the cardiac prognostic importance of GAD. Frasure-Smith and Lespérance²¹ demonstrated that GAD independently predicted cardiac events in 804 patients with acute coronary syndrome, but the extent to which the association was explained by potential behavioral and biological mediators was not assessed. Other studies^{11,15,18-26} examining the impact of anxiety on cardiac prognosis have relied on self-report measurements of anxiety symptoms and have varied in patient populations, sample size, length of follow-up, and ability to control covariates.

We previously found that the association between depressive symptoms and cardiovascular events was largely explained by poor health behaviors, especially physical inactivity, in depressed patients with CHD.²⁸ However, despite an exhaustive search for potential mediators, we did not identify the reason for an increased risk of cardiovas-

cular events associated with anxiety disorder. Several studies have demonstrated that anxiety is linked to pathologic mechanisms involved in CHD events,⁵¹ including indicators of autonomic dysfunction, such as reduced baroreflex cardiac control and reduced heart rate variability,⁵²⁻⁵⁵ increased catecholamine levels⁵⁶ and platelet activity,⁵⁷ dysregulation of the serotonin system,⁵⁸ and markers of inflammation and coagulation.⁵⁹ Thus, we were surprised that biological mediators, such as heart rate variability (SDANN), norepinephrine level, and inflammation (CRP level), did not explain the increased risk associated with anxiety disorder in the present study. Similarly, important health behaviors, including smoking, medication adherence, and physical activity, were not responsible for the increased risk of cardiovascular events.

This leaves the question of why GAD is associated with adverse outcomes in patients with CHD. One possibility is that anxiety may be associated with surges in catecholamines, which are, in turn, related to poor CHD prognosis. Although we collected urine samples to measure levels of catecholamines and found no association with GAD, it is possible that using 24-hour specimens did not allow us to capture these fluctuations. Another possibility is that anxious patients with CHD may be less likely to seek preventive medical care, possibly due to an avoidant coping strategy. Benninghoven et al⁶⁰ found that patients with higher anxiety levels had worse medication compliance and less contact with their cardiologists. Patients who are less likely to seek preventive care could be at increased risk for subsequent events. Alternatively, patients with anxiety could be more likely to seek care and receive a diagnosis of stroke or myocardial infarction, and, thus, the increased risk of events could be due to greater ascertainment in patients with anxiety. However, this would not explain their increased mortality. It is also possible that there exists a common background origin to GAD symptoms

and risk of cardiovascular disease. The interplay of genetic factors or the programming effects of fetal or postnatal growth patterns may play a role. Further research to determine the mechanisms responsible for the relationship between GAD and prognosis is warranted.

We also considered the possibility that depression could have interacted with anxiety and, thus, affected the relationship found between GAD and cardiovascular events. Anxiety and depression are highly comorbid disorders in psychiatric populations and in individuals with chronic medical conditions, including heart disease.⁶¹⁻⁶⁴ In the present study, 80% of patients with GAD had comorbid depressive disorder. However, adjusting for major depression did not change the effect of GAD on cardiovascular events, and we found no evidence of an interaction between GAD and depression. Therefore, the prognostic value of GAD seems to be independent of depressive disorder. This finding is consistent with 2 previous studies^{11,19} that found anxiety to be a significant predictor of cardiovascular events after adjustment for depression.

Finally, GAD was associated with lower ω -3 fatty acid levels. There is a clear association between dietary factors resulting in lower levels of ω -3 fatty acids and increased CHD risk.^{65,66} In addition, a recent study⁴³ found a strong association between low ω -3 fatty acid levels and depression in outpatients with stable CHD. Although ω -3 fatty acid levels did not affect the strength of association between GAD and cardiovascular events, this is a potentially interesting avenue to explore.

This study has several strengths, including detailed assessments of GAD and cardiac disease severity, careful measurement of potential behavioral and biological mediators, and comprehensive assessment of cardiovascular events. However, several limitations must also be considered. First, most of the participants were older men, and almost half were recruited from VA medical centers. Therefore, these results may not generalize to women or to other patient populations. Second, the associated risk with GAD may have been the result of greater cardiac disease severity. We attempted to address this possibility by carefully measuring and adjusting for comorbid conditions and cardiovascular disease severity. However, no observational study can completely eliminate confounding, and it remains possible that the effect of GAD on cardiovascular outcomes may have been affected by worse underlying cardiac disease severity that was not otherwise accounted for in the models. Third, this study was limited to outpatients with stable CHD, and, thus, we cannot comment on the mechanisms of association between anxiety and cardiovascular outcomes in healthy populations or in patients after acute coronary syndrome. Fourth, we did not account for other anxiety disorders, such as specific phobias, panic disorder, or posttraumatic stress disorder. In addition, the high comorbidity between GAD and MDD could also mean that minor variants of depression are prevalent that we did not account for in the analyses. Fifth, we had no information on the time frame between the qualifying CHD event and the assessment of GAD except that it was at least 6 months before enrollment.

Despite these limitations, these findings have implications for clinical practice and research. GAD may be considered a prognostic factor in patients with CHD and could

be used in risk stratification. Evaluation and treatment of anxiety may also be considered as part of the comprehensive management of patients with CHD. Research programs designed to advance our understanding of the impact of GADs on medical prognosis and biobehavioral mechanisms that link anxiety to mortality in the context of CHD are needed to develop evidence-based approaches to improving patient care. In particular, randomized clinical trials will be necessary to determine whether pharmacologic and behavioral interventions to reduce anxiety will result in better CHD outcomes. The management of anxiety in patients with CHD may also require the development of collaborative and integrative approaches combining medical and psychological expertise.

In summary, we found a strong and robust association between GAD and cardiovascular events that could not be explained by disease severity, health behaviors, or biological mediators. The results of this study indicate the need for future research to identify the underlying processes by which GAD contributes to adverse events in patients with CHD and to test interventions to alleviate this increased risk.

Submitted for Publication: July 23, 2009; final revision received December 10, 2009; accepted January 11, 2010.

Correspondence: Elisabeth J. Martens, PhD, Department of Medical Psychology, Tilburg University, Warandelaan 2, PO Box 90153, 5000 LE Tilburg, the Netherlands (e.j.martens@uvt.nl).

Author Contributions: Dr Whooley had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. **Financial Disclosure:** None reported.

Funding/Support: This study was supported by the VA Epidemiology (Merit Review) Program; the VA Health Services Research and Development service Career Development Program; grant R01 HL079235 from the National Heart, Lung, and Blood Institute; the American Federation for Aging Research (Paul Beeson Scholars Program); the Robert Wood Johnson Foundation (Generalist Physician Faculty Scholars Program); the Ischemia Research and Education Foundation; and the Nancy Kirwan Heart Research Fund (all funding to Dr Whooley).

Role of the Sponsors: The funding organizations had no role in the design or conduct of the study; in the collection, management, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript.

REFERENCES

1. Brotman DJ, Golden SH, Wittstein IS. The cardiovascular toll of stress. *Lancet*. 2007;370(9592):1089-1100.
2. Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, Blackett KN, Sitthi-amorn C, Sato H, Yusuf S; INTERHEART investigators. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364(9438):953-962.
3. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet*. 2007;370(9590):851-858.
4. Rugulies R. Depression as a predictor for coronary heart disease: a review and meta-analysis. *Am J Prev Med*. 2002;23(1):51-61.

5. Wulsin LR, Singal BM. Do depressive symptoms increase the risk for the onset of coronary disease? a systematic quantitative review. *Psychosom Med.* 2003; 65(2):201-210.
6. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med.* 2004;66(6):802-813.
7. van Melle JP, de Jonge P, Spijkerman TA, Tijssen JG, Ormel J, van Veldhuisen DJ, van den Brink RH, van den Berg MP. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom Med.* 2004;66(6):814-822.
8. Carney RM, Freedland KE, Jaffe AS. Depression as a risk factor for coronary heart disease mortality. *Arch Gen Psychiatry.* 2001;58(3):229-230.
9. Denollet J, Brutsaert DL. Personality, disease severity, and the risk of long-term cardiac events in patients with decreased ejection fraction after myocardial infarction. *Circulation.* 1998;97(2):167-173.
10. Thoms BD, Bass EB, Ford DE, Stewart KJ, Tsilidis KK, Patel U, Fauerbach JA, Bush DE, Ziegelstein RC. Prevalence of depression in survivors of acute myocardial infarction: review of the evidence. *J Gen Intern Med.* 2006;21(1):30-38.
11. Grace SL, Abbey SE, Irvine J, Shnek ZM, Stewart DE. Prospective examination of anxiety persistence and its relationship to cardiac symptoms and recurrent cardiac events. *Psychother Psychosom.* 2004;73(6):344-352.
12. Frasure-Smith N, Lespérance F, Talajic M. Depression and 18-month prognosis after myocardial infarction [published correction appears in *Circulation.* 1998 Feb 24;97(7):708]. *Circulation.* 1995;91(4):999-1005.
13. Frasure-Smith N, Lespérance F, Talajic M. The impact of negative emotions on prognosis following myocardial infarction: is it more than depression? *Health Psychol.* 1995;14(5):388-398.
14. Lane D, Carroll D, Ring C, Beevers DG, Lip GY. Mortality and quality of life 12 months after myocardial infarction: effects of depression and anxiety. *Psychosom Med.* 2001;63(2):221-230.
15. Mayou RA, Gill D, Thompson DR, Day A, Hicks N, Volmink J, Neil A. Depression and anxiety as predictors of outcome after myocardial infarction. *Psychosom Med.* 2000;62(2):212-219.
16. Sullivan MD, LaCroix AZ, Baum C, Grothaus LC, Katon WJ. Functional status in coronary artery disease: a one-year prospective study of the role of anxiety and depression. *Am J Med.* 1997;103(5):348-356.
17. Sullivan MD, LaCroix ZA, Spertus JA, Hecht J. Five-year prospective study of the effects of anxiety and depression in patients with coronary artery disease. *Am J Cardiol.* 2000;86(10):1135-1138, A6, A9.
18. Rothenbacher D, Hahmann H, Wüsten B, Koenig W, Brenner H. Symptoms of anxiety and depression in patients with stable coronary heart disease: prognostic value and consideration of pathogenetic links. *Eur J Cardiovasc Prev Rehabil.* 2007;14(4):547-554.
19. Shibeshi WA, Young-Xu Y, Blatt CM. Anxiety worsens prognosis in patients with coronary artery disease. *J Am Coll Cardiol.* 2007;49(20):2021-2027.
20. Moser DK, Riegel B, McKinley S, Doering LV, An K, Sheahan S. Impact of anxiety and perceived control on in-hospital complications after acute myocardial infarction. *Psychosom Med.* 2007;69(1):10-16.
21. Frasure-Smith N, Lespérance F. Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. *Arch Gen Psychiatry.* 2008;65(1):62-71.
22. Lane D, Carroll D, Ring C, Beevers DG, Lip GY. Effects of depression and anxiety on mortality and quality-of-life 4 months after myocardial infarction. *J Psychosom Res.* 2000;49(4):229-238.
23. Lane D, Carroll D, Ring C, Beevers DG, Lip GY. Do depression and anxiety predict recurrent coronary events 12 months after myocardial infarction? *QJM.* 2000; 93(11):739-744.
24. Lane D, Carroll D, Ring C, Beevers DG, Lip GY. In-hospital symptoms of depression do not predict mortality 3 years after myocardial infarction. *Int J Epidemiol.* 2002;31(6):1179-1182.
25. Ketterer MW, Huffman J, Lumley MA, Wassef S, Gray L, Kenyon L, Kraft P, Brymer J, Rhoads K, Lavallo WR, Goldberg AD. Five-year follow-up for adverse outcomes in males with at least minimally positive angiograms: importance of "denial" in assessing psychosocial risk factors. *J Psychosom Res.* 1998;44(2):241-250.
26. Herrmann C, Brand-Driehorst S, Buss U, Rüger U. Effects of anxiety and depression on 5-year mortality in 5057 patients referred for exercise testing. *J Psychosom Res.* 2000;48(4-5):455-462.
27. Whooley MA, de Jonge P, Vittinghoff E, Otte C, Moos R, Carney RM, Ali S, Dowray S, Na B, Feldman MD, Schiller NB, Browner WS. Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. *JAMA.* 2008;300(20):2379-2388.
28. Robins LN, Helzer J, Croughan J, Ratcliff K. National Institute of Mental Health Diagnostic Interview Schedule: its history, characteristics, and validity. *Arch Gen Psychiatry.* 1981;38(4):381-389.
29. Greist JH, Klein MH, Erdman HP, Bires JK, Bass SM, Machtiger PE, Kresge DG. Comparison of computer- and interviewer-administered versions of the Diagnostic Interview Schedule. *Hosp Community Psychiatry.* 1987;38(12):1304-1311.
30. Blouin AG, Perez EL, Blouin JH. Computerized administration of the Diagnostic Interview Schedule. *Psychiatry Res.* 1988;23(3):335-344.
31. Dawson DA, Grant BF, Stinson FS. The AUDIT-C: screening for alcohol use disorders and risk drinking in the presence of other psychiatric disorders. *Compr Psychiatry.* 2005;46(6):405-416.
32. Gehi AK, Ali S, Na B, Whooley MA. Self-reported medication adherence and cardiovascular events in patients with stable coronary heart disease: the Heart and Soul Study. *Arch Intern Med.* 2007;167(16):1798-1803.
33. Bowles HR, Fitzgerald SJ, Morrow JR Jr, Jackson AW, Blair SN. Construct validity of self-reported historical physical activity. *Am J Epidemiol.* 2004;160(3):279-286.
34. Kurtze N, Rangul V, Hustvedt BE, Flanders WD. Reliability and validity of self-reported physical activity in the Nord-Trøndelag Health Study: HUNT 1. *Scand J Public Health.* 2008;36(1):52-61.
35. Ainsworth BE, Jacobs DR Jr, Leon AS. Validity and reliability of self-reported physical activity status: the Lipid Research Clinics questionnaire. *Med Sci Sports Exerc.* 1993;25(1):92-98.
36. Aadahl M, Kjaer M, Kristensen JH, Møllerup B, Jørgensen T. Self-reported physical activity compared with maximal oxygen uptake in adults. *Eur J Cardiovasc Prev Rehabil.* 2007;14(3):422-428.
37. Jackson AW, Morrow JR Jr, Bowles HR, Fitzgerald SJ, Blair SN. Construct validity evidence for single-response items to estimate physical activity levels in large sample studies. *Res Q Exerc Sport.* 2007;78(2):24-31.
38. Gehi A, Mangano D, Pipkin S, Browner WS, Whooley MA. Depression and heart rate variability in patients with stable coronary heart disease: findings from the Heart and Soul Study. *Arch Gen Psychiatry.* 2005;62(6):661-666.
39. Otte C, Marmar CR, Pipkin SS, Moos R, Browner WS, Whooley MA. Depression and 24-hour urinary cortisol in medical outpatients with coronary heart disease: the Heart and Soul Study. *Biol Psychiatry.* 2004;56(4):241-247.
40. Otte C, Neylan TC, Pipkin SS, Browner WS, Whooley MA. Depressive symptoms and 24-hour urinary norepinephrine excretion levels in patients with coronary disease: findings from the Heart and Soul Study. *Am J Psychiatry.* 2005;162(11):2139-2145.
41. Wulsin LR, Musselman D, Otte C, Bruce E, Ali S, Whooley MA. Depression and whole blood serotonin in patients with coronary heart disease from the Heart and Soul Study. *Psychosom Med.* 2009;71(3):260-265.
42. Whooley MA, Caska CM, Hendrickson BE, Rourke MA, Ho J, Ali S. Depression and inflammation in patients with coronary heart disease: findings from the Heart and Soul Study. *Biol Psychiatry.* 2007;62(4):314-320.
43. Ali S, Garg SK, Cohen BE, Bhav P, Harris WS, Whooley MA. Association between omega-3 fatty acids and depressive symptoms among patients with established coronary artery disease: data from the Heart and Soul Study. *Psychother Psychosom.* 2009;78(2):125-127.
44. Ren X, Ristow B, Na B, Ali S, Schiller NB, Whooley MA. Prevalence and prognosis of asymptomatic left ventricular diastolic dysfunction in ambulatory patients with coronary heart disease. *Am J Cardiol.* 2007;99(12):1643-1647.
45. Asplund K, Bonita R, Kuulasmaa K, Rajakangas AM, Schaechlich H, Suzuki K, Thorvaldsen P, Tuomilehto J; World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease. Multinational comparisons of stroke epidemiology: evaluation of case ascertainment in the WHO MONICA Stroke Study. *Stroke.* 1995;26(3):355-360.
46. Thorvaldsen P, Asplund K, Kuulasmaa K, Rajakangas AM, Schroll M; World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease. Stroke incidence, case fatality, and mortality in the WHO MONICA project. *Stroke.* 1995;26(3):361-367.
47. Luepker RV, Apple FS, Christenson RH, Crow RS, Fortmann SP, Goff D, Goldberg RJ, Hand MM, Jaffe AS, Julian DG, Levy D, Manolio T, Mendis S, Mensah G, Pajak A, Prineas RJ, Reddy KS, Roger VL, Rosamond WD, Shahar E, Sharrett AR, Sorlie P, Tunstall-Pedoe H; AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; National Heart, Lung, and Blood Institute. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. *Circulation.* 2003;108(20):2543-2549.
48. Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, Katus HA, Newby LK, Ravkilde J, Chaitman B, Clemmensen PM, Dellborg M, Hod H, Porela P, Underwood R, Bax JJ, Beller GA, Bonow R, Van der Wall EE, Bassand JP, Wijns W, Ferguson TB, Steg PG, Uretsky BF, Williams DO, Armstrong PW, Antman EM, Fox KA, Hamm CW, Ohman EM, Simoons-Sel ML, Poole-Wilson PA, Gurfinkel EP, Lopez-

- Sendon JL, Pais P, Mendis S, Zhu JR, Wallentin LC, Fernández-Avilés F, Fox KM, Parkhomenko AN, Priori SG, Tendera M, Voipio-Pulkki LM, Vahanian A, Camm AJ, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellems I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Morais J, Brener S, Harrington R, Morrow D, Lim M, Martinez-Rios MA, Steinhilb S, Levine GN, Gibler WB, Goff D, Tubaro M, Dudek D, Al-Attar N; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Circulation*. 2007;116(22):2634-2653.
49. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol*. 1986;51(6):1173-1182.
 50. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. *Am J Epidemiol*. 1993;138(11):923-936.
 51. Grippo AJ, Johnson AK. Biological mechanisms in the relationship between depression and heart disease. *Neurosci Biobehav Rev*. 2002;26(8):941-962.
 52. Thayer JF, Friedman BH, Borkovec TD. Autonomic characteristics of generalized anxiety disorder and worry. *Biol Psychiatry*. 1996;39(4):255-266.
 53. Martens EJ, Nyklicek I, Szabó BM, Kupper N. Depression and anxiety as predictors of heart rate variability after myocardial infarction. *Psychol Med*. 2008;38(3):375-383.
 54. Watkins LL, Blumenthal JA, Carney RM. Association of anxiety with reduced baroreflex cardiac control in patients after acute myocardial infarction. *Am Heart J*. 2002;143(3):460-466.
 55. Cohen H, Benjamin J. Power spectrum analysis and cardiovascular morbidity in anxiety disorders. *Auton Neurosci*. 2006;128(1-2):1-8.
 56. Cameron OG, Nesse RM. Systemic hormonal and physiological abnormalities in anxiety disorders. *Psychoneuroendocrinology*. 1988;13(4):287-307.
 57. Cameron OG, Smith CB, Lee MA, Hollingsworth PJ, Hill EM, Curtis GC. Adrenergic status in anxiety disorders: platelet alpha 2-adrenergic receptor binding, blood pressure, pulse, and plasma catecholamines in panic and generalized anxiety disorder patients and in normal subjects. *Biol Psychiatry*. 1990;28(1):3-20.
 58. Williams RB, Marchuk DA, Gadde KM, Barefoot JC, Grichnik K, Helms MJ, Kuhn CM, Lewis JG, Schanberg SM, Stafford-Smith M, Suarez EC, Clary GL, Svenson IK, Siegler IC. Central nervous system serotonin function and cardiovascular responses to stress. *Psychosom Med*. 2001;63(2):300-305.
 59. Pitsavos C, Panagiotakos DB, Papageorgiou C, Tsetsekou E, Soldatos C, Stefanadis C. Anxiety in relation to inflammation and coagulation markers, among healthy adults: the ATTICA study. *Atherosclerosis*. 2006;185(2):320-326.
 60. Benninghoven D, Kaduk A, Wiegand U, Specht T, Kunzendorf S, Jantschek G. Influence of anxiety on the course of heart disease after acute myocardial infarction: risk factor or protective function? *Psychother Psychosom*. 2006;75(1):56-61.
 61. Zimmerman M, McDermt W, Mattia JI. Frequency of anxiety disorders in psychiatric outpatients with major depressive disorder. *Am J Psychiatry*. 2000;157(8):1337-1340.
 62. Katon W, Lin EHB, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. *Gen Hosp Psychiatry*. 2007;29(2):147-155.
 63. Aina Y, Susman JL. Understanding comorbidity with depression and anxiety disorders. *J Am Osteopath Assoc*. 2006;106(5)(suppl 2):S9-S14.
 64. Walke LM, Byers AL, Gallo WT, Endress J, Fried TR. The association of symptoms with health outcomes in chronically ill adults. *J Pain Symptom Manage*. 2007;33(1):58-66.
 65. Marchioli R, Barzi F, Bomba E, Chieffo C, Di Gregorio D, Di Mascio R, Franzosi MG, Geraci E, Levantesi G, Maggioni AP, Mantini L, Marfisi RM, Mastrogiuseppe G, Mininni N, Nicolosi GL, Santini M, Schweiger C, Tavazzi L, Tognoni G, Tucci C, Valagussa F; GISSI-Prevenzione Investigators. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI) – prevenzione. *Circulation*. 2002;105(16):1897-1903.
 66. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K; Japan EPA Lipid Intervention Study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis [published correction appears in *Lancet*. 2007;370(9583):220]. *Lancet*. 2007;369(9567):1090-1098.